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Toxic interaction between Th2 cytokines and *Staphylococcus aureus* in atopic dermatitis

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Abstract

Patients with atopic dermatitis (AD) are commonly colonized/infected with *Staphylococcus aureus*, and this bacterium is known to worsen the dermatitis. In this issue, Brauweiler *et al.* demonstrate a newly discovered mechanism by which Th2 cytokines involved in AD augments the toxicity of the lytic staphylococcal protein alpha toxin. This review presents mechanisms by which Th2 cytokines may interact with *S. aureus* to the detriment of the dermatitis.

The vast majority (~90%) of individuals with active atopic dermatitis (AD) are colonized/infected with *Staphylococcus aureus*, a species implicated in worsening the skin disease. The propensity of these patients to harbor staphylococcal bacteria is thought to be due in part to the inhibitory effects of Th2 cytokines (IL-4, IL-13) on antimicrobial peptide production. Through this mechanism and the inhibitory effects of these cytokines on barrier formation, Th2 cytokines provide an environment conducive to bacterial growth.

Given their clinical importance in the management of AD, the mechanisms by which staphylococcal bacteria worsen AD are areas of active study. Staphylococcal bacteria trigger inflammation from direct infection of cell types such as keratinocytes. Staphylococcal products can also exert profound effects via binding to specific receptors. With examples listed in Table I, these agents include exotoxins that act as superantigens, staphylococcal protein A, the cell wall product lipoteichoic acid, and cytolytic toxins such as staphylococcal alpha toxin and delta toxin. The exact importance of these staphylococcal products in AD associated with infection is, as yet, unknown.

Superantigens including Toxic Shock Syndrome Toxin-1 (TSST-1) and Staphylococcal enterotoxin B (SEB) have significant pro-inflammatory effects via their abilities to bind to MHCII molecules and activate large numbers of T cells. Relevant to AD, many patients harbor specific IgE antibodies that recognize these large globular proteins (Leung *et al*., 1993). Thus, superantigen-producing *S. aureus* could generate type I allergic responses via this mechanism. Staphylococcal Protein A (SPA), a surface protein, acts as an important, yet complex, virulence factor contributing to the success of this pathogen by interfering with immune clearance and by modulating inflammation in part via its ability to activate the TNF

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receptor 1 (TNFR1) directly. Although this would be expected to engender a pro-inflammatory response, recent studies have suggested that through triggering of TNFR1 shedding, SPA can actually exert anti-inflammatory effects by the removal of local TNF-α (Giai *et al*., 2013). The cell wall component lipoteichoic acid (LTA) has also been implicated in AD inflammation. Recent studies indicate that large (microgram) amounts of this toll-like receptor 2- and Platelet-activating factor receptor agonist are found on the skin of children with secondarily infected AD (Travers *et al*., 2010).

Staphylococcal bacteria also commonly express at least four cytolytic toxins that appear to play important roles in virulence as well as in host damage/inflammation. For example, recent studies have determined that delta toxin is a potent inducer of mast cell degranulation (Nakamura *et al*., 2013). Although IgE is not necessary for delta toxin-mediated mast cell degranulation, the presence of this allergy-associated antibody on mast cell results in exaggerated toxin responses (Nakamura *et al*., 2013). Thus, AD patients with high levels of IgE in response to Th2 cytokine overactivity would be especially susceptible to delta toxin-mediated effects.

Staphylococcal alpha toxin is one of the most prominent and destructive cytolytic toxins. This pore-forming toxin can act on cell membranes directly, and this process appears to be facilitated via binding to membrane sphingomyelin molecules. Alpha toxin treatment of keratinocytes induces cytokine production as well as inducing cellular death (Ezepchuk *et al*., 1996; Travers *et al*., 2003). As reported in this issue, Brauweiler and colleagues provide evidence that Th2 cytokine exposure can increase the sensitivity of keratinocytes to alpha toxin-mediated cell death (Brauweiler *et al*., 2014). Alpha toxin treatment of skin biopsies derived from AD patients resulted in increased levels of cell death in comparison with normal skin. The role of Th2 cytokines was then confirmed using keratinocyte primary cultures treated with IL-4/IL-13. In contrast, gamma-interferon treatment did not modulate alpha toxin-mediated cytotoxicity. IL-4/IL-13 augmentation of alpha toxin-mediated cytotoxicity was shown to be due to the ability of these Th2 cytokines to decrease levels of acid sphingomyelinase, the enzyme that cleaves sphingomyelin into ceramide and phosphocholine. The ability of exogenous sphingomyelinase or phosphocholine to reverse the alpha toxin toxicity not only confirmed the mechanisms, but, also provided the rationale for possible therapeutics.

The authors also demonstrated in a recent companion report that the epidermal barrier protein filaggrin also plays an important role in the regulation of acid sphingomyelinase, and that deficiency inf filaggrin predisposes for increased alpha toxin-mediated cytotoxicity (Brauweiler *et al*., 2013). Relevant to Th2 cytokines, IL-4 and IL-13 have also been shown to inhibit filaggrin expression (Howell *et al*., 2009). Thus, one can envision a positive feedback pathway by which Th2 cytokines not only provide a permissive environment for *S. aureus*, but, also enhance the effects of staphylococcal products. These findings are compatible with the notion that strategies that remove bacteria such as dilute bleach baths can improve AD skin disease (Huang *et al*., 2009).

In summary, the interplay between Th2 cytokines and *S. aureus* has high significance for understanding AD. Indeed, the majority of AD flares involve *S. aureus* in some capacity.

New insights into the exact mechanisms by which staphylococcal exposure can worsen AD could allow improved and novel treatments for this common skin disease and its significant morbidities.

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Clinical Implications

Staphylococcal infection is a known trigger for worsening of atopic dermatitis skin disease, likely through multiple mechanisms.

These studies describe a novel mechanism by which Th2 cytokines associated with atopic dermatitis patients can worsen the effects of alpha toxin, a major cytotoxic protein produced by *Staphylococcus aureus*.

The ability to block the effects of alpha toxin via use of exogenous acid sphingomyelinase or phosphocholine provides the impetus for novel therapeutics to treat atopic dermatitis patients with chronic skin staphylococcal infections.

Table I

Mechanisms by which staphylococcal products can modulate AD and role of Th2 cytokines.

Staphylococcal Mediator	Effect on AD Skin Lesion	Th2 cytokine effect	References
Alpha toxin	Increased keratinocyte cell death and worsening of lesion; increased cytokine production	Increased toxicity via inhibiting filaggrin, acid sphingomyelinase	Brauweiler *et al*., 2013, 2014
Delta toxin	Increased mast cell degranulation and worsening of lesion	Increased effect via increased IgE production	Nakamura *et al*., 2013
Superantigen (SEB, TSST-1…)	Increased mast cell degranulation and release of cytokines via triggering specific IgE molecules and worsening of lesion	Increased effect via increased IgE production	Leung *et al*., 1993
Staphylococcal Protein A	Unclear effects; Increased inflammation via signaling through TNFR1 versus anti-inflammatory effects via removal of TNF-α	Not known	Giai *et al*., 2013
Lipoteichoic acid	Increased inflammation via signaling through TLR2 and Platelet-activating factor receptor and worsening of lesion	Not known	Travers *et al*., 2010